Remarks

Claims 1-14 were previously pending in the subject application. As an initial matter, the applicants confirm the election of Group I and acknowledge that claims 10-12 are withdrawn from consideration at this time. By this Amendment, claims 1, 8, 9 and 13 have been amended, claims 10-12 have been withdrawn as relating to non-elected subject matter, and new claims 15 and 16 have been added. Accordingly, claims 1-9 and 13-16 are now before the Examiner for consideration.

Support for the amendments to the claims can be found throughout the specification, particularly at page 6, lines 11-21 and Test Examples 1-9. In this regard, as is well known to those skilled in the art, antibodies bind to proteins so the term "MK levels" as it is used throughout the examples clearly refers to levels of MK protein. Further support for the amendments can be found at page 5, lines 2-5, the mutant is further described by Kaname T. *et al.*: Biochem. Biophys. Res. Commun., 219: 256-260, 1996, the contents of which are incorporated by reference in the instant specification; and at page 3, line 1-8 and Example 2 (beginning at page 14, line 36).

Please note that the amendments set forth herein have been done to lend greater clarity to the claims and to expedite prosecution. These amendments should not be taken to indicate the applicants' agreement with, or acquiescence to, the rejections of record. Favorable consideration of the claims now presented, in view of the remarks and amendments set forth herein, is earnestly solicited.

The applicants did not receive a copy of the initialed PTO Form 1449 (Paper No. 12) as indicated in the Office Action Summary. The applicants respectfully request that the Examiner forward an initialed copy of the PTO Form 1449 (Paper No. 12).

In the Office Action, the title has been objected to as not being sufficiently descriptive of that which is claimed. The applicants appreciate the Examiner's helpful remarks. Accordingly, the applicants have amended the title to more accurately describe that which is claimed. Therefore, withdrawal of this objection is respectfully requested.

Claims 1-9, 13 and 14 have been rejected under 35 U.S.C 112, first paragraph, for failing to comply with the written description requirement. Specifically, the Office Action states that the claims, directed to measuring the level of MK, or a fragment thereof, are not commensurate in scope

with the specification, which describes full length human MK. It is stated in the Office Action that the specification fails to demonstrate possession of "any and all MK molecules, which encompass molecules from any species of animal, as well as mutant MK".

Without agreeing with the underlying basis for this rejection, but in order to expedite prosecution and better define the literal scope of the claims (without surrendering any subject matter that may be covered under the Doctrine of Equivalents) the applicants have amended their claims herein to recite a "human midkine protein and a human midkine protein that lacks a domain near the N-terminus" instead of a "midkine, or a fragment thereof".

Human midkine is known in the art as a retinoic acid-responsive gene product and heparin-binding growth/differentiation factor, a 13-kDa polypeptide rich in basic amino acids and cysteines whose full length DNA sequence is known in the art. See, for example, U.S. Patent No: 5,461,029; Kadomatsu, K. *et al.*: Biochem. Biophys. Res. Commun., 151: 1312-1318; Tomomura, M. et al.: J. Biol. Chem., 265: 10765-10770, 1990 and the instant specification at page 1, lines 28-33. Likewise, human midkine protein lacking an N-domain is known in the art and has been demonstrated to be expressed cancer-specifically. See Kaname T. *et al.*: Biochem. Biophys. Res. Commun1, 219: 256-260, 1996 (specifically, Kaname teaches a mutant human midkine lacking Exon 3) and the instant specification at page 5, lines 2-5. Accordingly, the genus claimed in the amended claims does not have substantial variation. Moreover, the two disclosed species are sufficiently representative of the genus to demonstrate possession thereof.

Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, based on the written description requirement.

Claims 1-9, 13, and 14, have also been rejected under 35 USC 112, first paragraph. It is stated in the Office Action that the specification, while being enabling for methods involving the step of measuring the level of human midkine protein in a biological sample, does not reasonably provide enablement for methods involving measuring the level of a midkine mutant or midkine fragment. As discussed below, the applicants respectfully submit that the pending claims are fully enabled.

The applicants respectfully submit that the claims, as originally filed, were fully enabled; however, to expedite prosecution the claims have been amended, as described above, to lend greater clarity to the claimed subject matter. The applicants respectfully submit that these amendments have rendered moot this enablement rejection. Thus, as amended, the scope of the claims is commensurate with the scope of the enabling disclosure. Specifically, both human midkine and the human midkine mutant that lacks an N-domain have been demonstrated, either by the applicants or by other researchers, to be expressed in a cancer specific manner and, accordingly, may readily be used in accordance with the subject invention for the detection of early cancer and the assessment of cancer prognosis as claimed. See, for example, the Test Examples 1-9 of the instant specification (pages 15-21) as well as Kaname T. *et al.*, Biochem. Biophys. Res. Commun., 219: 256-260, 1996. Thus, one skilled in the art could readily perform the methods of the claimed invention from the disclosures in the instant patent application, coupled with information known in the art, without undue experimentation.

Thus, the applicants respectfully request reconsideration and withdrawal of the enablement rejection under 35 U.S.C. §112, first paragraph.

Claims 1-9, 13 and 14 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as the invention.

Specifically, the Office Action states that:

> With respect to claims 1, 9, and 13, the recitation of "the level of midkine" is unclear as it is not clear what form of midkine is to be detected (i.e., mRNA, DNA, protein, etc.);
> With respect to claims 1, 2, 4, 6, and 9, the recitation of early cancer is vague and indefinite; and
> With respect to claim 13, the method step of "correlating" is vague and indefinite.

With regards to item (a), to expedite prosecution, the applicants have amended claims 1, 9, and 13 to refer to the "level of human midkine protein." This clarifying amendment is not meant to limit the scope of the applicants' claims.

With regards to item (b), the applicants have expressly defined the noted term at page 4, lines 16-28 as follows:

> *"Early cancer" refers to tumors confined to the site of development (intramucosal) that have not invaded surrounding tissues, or those that have invaded, but the range of invasion is confined to a local area. Especially, tumors showing no invasion are important detection targets in the present invention since they have been difficult to detect by well-known tumor markers. This definition is applicable to almost all cancers such as those of the skin, oral cavity, respiratory tract, gastrointestinal tract, uterine cervix, ovary, gallbladder, bladder, and such. Early cancer includes stage 0 (carcinoma in situ) and stage I according to the TNM classification. In these cancer stages, there are no intravascular invasions or distant metastases, and local tumor ablation alone will lead to complete recovery.*

The test for indefiniteness is whether one of ordinary skill in the art would understand the bounds of the claim, when read in light of the specification and in the context of the prior art. Thus, claim language cannot be analyzed in a vacuum but must be interpreted in light of the specification, the teachings of the prior, and the reasonable interpretation given by one of ordinary skill.

Accordingly, from the above teachings in the instant specification, one of ordinary skill in the art would readily understand the bounds of the claim and would clearly be capable of differentiating between a normal person without cancer and a person having early cancer even though both may be asymptomatic at the time of assessment. Moreover, contrary to what is stated in the Office Action, in the context of the present invention, and in light of the definition provided in the application, the term "early" does indeed aid in classifying or staging the cancer.

With regard to item (c), to expedite prosecution, claim 13 has been amended herein to include the step of comparing the measured MK level after treatment to that measured prior to treatment, wherein a decrease in MK level correlates to a positive prognosis.

The applicants appreciate the Examiner's helpful comments regarding the clarity of the claims. In view of the remarks and amendments as set forth herein, the applicants respectfully submit that the metes and bounds of the claims would be readily discernable to one skilled in the art.

Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

Claims 1, 9 and 13 have been rejected under 35 U.S.C. 102(b) as being anticipated by Ye *et al.* (British Journal of Cancer 79(1): 179-184, January 1999/Reference R2 from IDS Paper number 9). The applicants respectfully traverse this ground for rejection because the cited reference does not disclose the invention as claimed.

Many court decisions have clearly established that rejections under 35 USC §102 are appropriate only in those instances where a single prior art reference has placed into the public domain the very invention which is claimed. In *Lindemann v. American Hoist and Derrick Co.*, 221 USPQ 481 (Fed. Cir. 1984), the court stated:

> Anticipation requires the presence in a single prior art reference, disclosure of each and every element of the claimed invention, arranged as in the claim. *Connell v. Sears Roebuck and Co.*, 722 F.2d 1542, 220 USPQ 193 (Fed. Cir. 1983); *SSIH Equip. S.A. v. USITC*, 718 F.2d 365, 216 USPQ 678 (Fed. Cir. 1983). In deciding the issue of anticipation, the [examiner] must identify the elements of the claims, determine their meaning in light of the specification and prosecution history, and identify corresponding elements disclosed in the allegedly anticipating reference. *SSIH, supra*; *Kalman [v. Kimberly-Clarke*, 713 F.2d 760, 218 USPQ 781 (Fed. Cir. 1983)] (emphasis added). 221 USPQ at 485.

In *Dewey & Almy Chem. Co. v. Mimex Co.*, Judge Learned Hand wrote:

> No doctrine of the patent law is better established than that a prior patent . . . to be an anticipation must bear within its four corners adequate directions for the practice [of the subsequent invention] . . . if the earlier disclosure offers no more than a starting point . . . if it does not inform the art without more how to practice the new invention, it has not correspondingly enriched the store of common knowledge, and it is not an anticipation. 124 F.2d 986, 990; 52 USPQ 138 (2nd Cir. 1942).

The Ye *et al.* reference does not disclose, within its four corners, the highly advantageous assay for the detection of early cancer as claimed by the current applicants. Accordingly, an anticipation rejection is not proper and the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) based on the Ye *et al.* reference.

Claims 1-5, 9, 13 and 14 have been rejected under 35 U.S.C. 102(b) as being anticipated by Aridome *et al.* (Jpn. J. Cancer Res. 86:665-661, 1995/Reference R1 from IDS, Paper number 12).

The applicants respectfully traverse this grounds for rejection because the cited reference does not disclose the invention as claimed.

The Aridome *et al.* reference does not disclose, within its four corners, the highly advantageous assay for the detection of early cancer as claimed by the current applicants. Accordingly, an anticipation rejection is not proper and the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) based on the Aridome *et al.* reference.

Claims 1-7, 13 and 14 have been rejected under 35 U.S.C. 102(b) as being anticipated by Tsutsui *et al.* (Cancer Research 53:1281-1285, March 15, 1993/Reference R7 from IDS, Paper number 12). The applicants respectfully traverse this grounds for rejection because the cited reference does not disclose the invention as claimed.

The Tsutsui *et al.* reference does not disclose, within its four corners, the highly advantageous assay for the detection of early cancer as claimed by the current applicants. Accordingly, an anticipation rejection is not proper and the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) based on the Tsutsui *et al.* reference.

Claims 1, 4, 5, 8, 9, 13 and 14 have been rejected under 35 U.S.C. 102(b) as being anticipated by Muramatsu *et al.* (J. Biochem. 119:1171-1175, 1996/Reference R6 from IDS, Paper number 12). The applicants respectfully traverse this grounds for rejection because the cited reference does not disclose the invention as claimed.

Muramatsu *et al.* do not describe detection of "early" cancer and thus cannot anticipate the instant claims that clearly recite this limitation. In addition, Muramatsu *et al.* do not disclose or suggest the one-step sandwich enzyme assay of the present invention. Nor do they disclose any weaknesses or deficiencies of their assay method, and therefore, a skilled artisan would not be motivated to modify the Muramatsu *et al.* method to reach the method of the instant invention. Accordingly, the applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. §102(b) based on the Muramatsu *et al.* reference.

Claims 1 and 13 have been rejected under 35 U.S.C. 102(b) as being anticipated by Nakagawara *et al.* (Cancer Research 55(8): 1792-1797, April 5, 1995/Reference R1 from IDS, Paper number 9). The applicants respectfully traverse this grounds for rejection because the cited reference does not disclose the invention as claimed.

The Nakagawara *et al.* reference does not disclose, within its four corners, the highly advantageous assay for the detection of early cancer as claimed by the current applicants. Accordingly, an anticipation rejection is not proper and the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) based on the Nakagaware *et al.* reference.

Claims 1-9, 13 and 14 have been rejected under 35 U.S.C. 102(a) as being anticipated by Ikematsu *et al.* (British Journal of Cancer 83(6): 701-706, September 2000/Reference R3 from IDS, Paper number 12). The applicants respectfully traverse this grounds for rejection.

Please note that, the present application has an effective filing date of September 10, 1999. Accordingly, as the Ikematsu *et al.* reference was published after the filing date of the present application, it cannot qualify as prior art. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 USC 102(b) based on the Ikematsu *et al.* reference.

As noted above, in order to anticipate a claim, a single reference must disclose each and every element claimed. In this case, none of the cited references, upon which anticipation rejections have been based, disclose or suggest the use of a one-step sandwich enzyme immunoassay, as is required by the claims that are currently presented for examination. Nor would the claimed invention have been obvious in view of these references, alone or in combination. The simple and highly sensitive assay of the claimed invention provides for highly sensitive detection of MK levels appearing in the body fluid of patients at an early stage of various cancers. The assay can be completely automated and is extremely useful as a method for measuring MK that aims at early cancer detection. [See specification at page 3, lines 1-8.] As compared to previously disclosed assays, the present method is advantageous in that detection can be noted by a simple color change,

making it much more convenient for clinical use. [See Ikematsu et al. (2000), page 705, column 1 (first paragraph in the discussion section)].

As the references cited above fail to disclose one or more elements of the instant claims, they cannot anticipate the inventions claimed in claims 1-9, 13, and 14. Accordingly, the rejections under 35 USC 102(b) should be withdrawn.

Claims 1-5, 8, 9, 13 and 14 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Aridomee *et al.* (JPN. J. Cancer Res. 86:655-661, 1995/Reference R1 from IDS, Paper number 12), in view of Muramatsu *et al.* (J. Biochem. 119:1171-1175, 1996/Reference R6 from IDS, Paper number 12. Also, claims 1-9, 13 and 14 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Tsutsui *et al.* (Cancer Research 53:1281-1285, March 15, 1993/Reference R7 from IDS, Paper number 12), in view of Muramatsu *et al.* (J. Biochem. 119:1171-1175, 1996/Reference R6 from IDS, Paper number 12). The applicants respectfully traverse these grounds for rejection because the cited references, alone or in combination, do not disclose or suggest the applicants' unique and advantageous methods for quickly, easily and accurately detecting early cancer.

As noted above, the claimed invention would not have been obvious in view of these references, alone or in combination. The simple and highly sensitive assay of the claimed invention provides for highly sensitive detection of MK levels appearing in the body fluid of patients at an early stage of various cancers. The assay can be completely automated and is extremely useful as a method for measuring MK that aims at early cancer detection. As compared to previously disclosed assays, the present method is advantageous in that detection can be noted by a simple color change, making it much more convenient for clinical use.

It has been well established in the patent law that the mere fact that the purported prior art could have been modified or applied in some manner to yield applicant's invention would not have made the modification or application obvious unless the prior art suggested the desirability of the modification. *In re Gordon*, 221 USPQ 1125, 1127 (Fed. Cir. 1984). As expressed by the CAFC, to support a §103 rejection, "[b]oth the suggestion and the expectation of success must be founded in the prior art . . . ." *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988) (emphasis added). As is clearly shown by the foregoing remarks, one finds neither the suggestion nor the

expectation of success in the cited references, either separately or combined. An assertion of obviousness without the required suggestion or expectation of success in the prior art is tantamount to using applicant's disclosure to reconstruct the prior art to arrive at the subject invention. Hindsight reconstruction of the prior art cannot support a §103 rejection, as was specifically recognized by the CCPA in *In re Sponnoble*, 56 CCPA 823, 160 USPQ 237, 243 (1969).

Aridome *et al.* and Tsutsui *et al.* both use the Northern Blot method to detect MK. Neither Aridome *et al.* nor Tsutsui *et al.* nor Muramatsu *et al.* disclose or suggest the advantageous use of a one-step sandwich enzyme assay to measure the level of MK protein in a body fluid, as is required by the claims as amended. Thus, even assuming *arguendo* that the noted combinations were proper, they would not result in the invention as claimed.

Please note that newly added claims 15 and 16 recite a one-step sandwich enzyme immunoassay that includes an avian anti-human midkine antibody and a rabbit anti-human midkine antibody to measure the level of MK protein in a body fluid. The combination of avian and rabbit anti-human MK antibodies results in an assay that exhibits a much higher sensitivity in the detection of human MK than other conventional assays, such as those utilizing rabbit antibodies alone. Without wishing to be bound by theory, this is most likely due to the fact that the major epitopes recognized by avian antibodies are different from those recognized by rabbit antibodies. Accordingly, the two antibodies do not antagonize each other and thus are especially suitable for the instant method.

In view of the distinctions between the cited references and the claimed invention, as well as the important advantages of the claimed method for the efficient and easy detection of early cancer, the current claims cannot reasonably be said to be obvious in view of the cited references. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejections under 35 USC 103.

In view of the foregoing remarks and the amendment above, the applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

The applicant also invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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